Endocrine Management of Gender Dysphoria in Adults

Prescribing Guidance for Non-specialist Practitioners

November 2019
This document has been prepared by Dr Sophie Quinney, GP with Specialist Interest, with support from the All Wales Prescribing Advisory Group (AWPAG) and the All Wales Therapeutics and Toxicology Centre (AWTTC), and has subsequently been endorsed by the All Wales Medicines Strategy Group (AWMSG).

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GLOSSARY

Cisgender
A person whose gender identity corresponds with the sex assigned at birth.

Gender dysphoria
The discomfort or distress that some trans people experience as a result of the incongruence between their gender identity and sex assignment at birth.

Non-binary
A non-binary person has a gender identity that is neither (exclusively) male nor female.

Trans men
Individuals assigned female at birth who identify as men.

Transsexualism
The diagnostic term Transsexualism (ICD-10) is soon to be replaced with Gender Incongruence (ICD-11), which refers to a marked and persistent incongruence between an individual’s experienced gender and assignment at birth.

Trans women
Individuals assigned male at birth who identify as women.
1.0 INTRODUCTION

This document is intended for non-specialist practitioners engaged in the prescribing and monitoring of medical therapies used in the management of gender dysphoria.

It recommends some medicines for indications for which they do not have a UK marketing authorisation at the time of publication. In these situations, the prescriber should follow relevant specialist professional guidance. For more information on the use of medicines outside their licensed indications (‘off-label use’), see the General Medical Council’s ‘Good practice in prescribing and managing medicines and devices’.

The Interim Gender Dysphoria Protocol and Service Guideline 2013/14 for NHS England outlines the following criteria, all of which are required to be met before a person starts hormone treatment.

- Persistent, well-documented gender dysphoria.
- Capacity to make a fully informed decision and to consent to treatment.
- Aged at least 17 years.
- If significant medical or mental health concerns are present, these must be reasonably well controlled.

The patient will have completed an assessment with a suitably qualified Welsh Gender Team clinician, and a diagnosis of Gender Dysphoria (DSM-V), Transsexualism (ICD-10) or Gender Incongruence (ICD-11) established.

A treatment recommendation should only be made after a specialist clinician has counselled the patient about the physical and emotional changes that can be anticipated, the risks and limitations of treatment, and the potential impact on their reproductive options. Gamete preservation will ideally have been completed if desired, and the patient offered appropriate sexual health and contraceptive advice.

The non-specialist practitioner should be provided with a copy of the patient consent form, written information regarding the name of the medicine(s) recommended, dose and route of administration, and additional information relevant to the treatment course.

At the time of writing, Local Gender Team (LGT) non-specialist practitioners are responsible for the initiation and optimisation of hormone therapies and will receive patients directly into their care from the Welsh Gender Team.

Once optimisation criteria are met, the patient’s General Practitioner is invited to provide maintenance treatment on a long-term basis supported by a Directed Enhanced Service (see Appendix 1), and advice from the Welsh Gender Team who can be contacted by phone or email (contact details provided on page 17).

To ensure a seamless supply of prescribed medication and avoid interruptions to the regimen, liaise with the local dispensing pharmacy at the earliest opportunity.

* It is intended to support prescribing for patients endorsed by an NHS Gender Identity clinic. For advice on bridging, harm reduction, and prescribing on behalf of private sector clinicians, please go to www.gpone.wales.nhs.uk/bridging-self-medication-and-the-private
2.0 PATHWAY FOR PEOPLE AGED OVER 17.5 YEARS WISHING TO ACCESS THE WELSH GENDER SERVICE

Patient asks their registered GP for a referral to the Welsh Gender Service.

GP completes referral form and sends it via Welsh Clinical Communications Gateway (WCCG) to the Welsh Gender Service.

Welsh Gender Team confirm receipt of referral with the patient.

Patient receives information pack from Welsh Gender Team and, if appropriate, may request referral for gamete preservation from their GP.

Welsh Gender Team requests baseline blood test with GP within 3 months of first appointment at the tertiary clinic.

Diagnostic evaluation conducted by Welsh Gender Team. Patients with complex needs may be referred to Charing Cross for ongoing care.

If hormone therapy is indicated, Local Gender Team prescriber to initiate treatment, then for discharge to own GP (or alternative prescriber) for maintenance of treatment under Directed Enhanced Service once optimisation criteria are met.

Patient assigned male at birth

- Estradiol
  - Estrogen supplementation
- +/- Gonadotrophin releasing hormone agonist
  - If suppression of natal hormone required
- Optional adjunct: Finasteride

Patient assigned female at birth

- Testosterone
  - Androgen supplementation
- Optional adjunct: Medroxyprogesterone acetate

Welsh Gender Team may refer for “late notice” gamete preservation, speech and language therapy, and specialist psychology/counselling at the request of the patient.
3.0 TESTOSTERONE THERAPY – PRESCRIBING NOTES

For most trans men, the aim of hormone therapy is to achieve serum testosterone levels equivalent to the adult male range, and in doing so simulate male puberty, a process that can take up to 5 years to complete.

Some (but not all) non-binary individuals assigned female at birth use low dose testosterone therapy under specialist guidance.

Testosterone is neither a contraceptive nor does it prevent sexually transmitted infections.

Treatment should start with gel (or in some cases a short-acting injection), moving to a long-acting injectable formulation provided that blood monitoring test results are satisfactory, and the patient wishes to do so.

Gels offer more control and predictability but can be messy and require daily application. Short-acting injectable preparations can be self-administered but are associated with a larger variation in testosterone levels over the cycle of administration and are therefore less preferred to the long-acting injectable preparation for long-term use.

Full dose testosterone alone is usually sufficient to suppress menstruation after 3 to 6 months. It is good practice to offer high-dose progestin (medroxyprogesterone acetate [Provera®] 10 mg twice daily to maximum of three times daily), for up to 6 months either at the start of testosterone treatment if desired, or if menstrual bleeding is not arrested once the target testosterone range is achieved.

Non-binary individuals assigned female at birth who use testosterone at lower doses may require longer term suppression of menses, e.g. a depot or intrauterine progestin.

If menstrual suppression with this type of medication is ineffective, contraindicated, or not desired, a gonadotrophin-releasing hormone (GnRH) agonist can be considered with support from the Welsh Gender Team. This is discussed in Section 5.0.

Smoking further compounds the risk of polycythaemia associated with exogenous androgen use, so cessation should be strongly encouraged. The decision to commence treatment in a patient who smokes should be made by the Welsh Gender Team.

Before starting testosterone therapy, a patient should ideally have stopped smoking for a minimum of 3 months. Nicotine replacement therapy (NRT) is considered a safe alternative in this scenario. It is good practice to document smoking status at each clinical review and to be alert to the possibility if a significant rise in haematocrit is observed during routine monitoring*.

Inform the Welsh Gender Team if a patient has had a break from testosterone treatment of longer than six months.

* If a patient reports that they have resumed smoking, encourage cessation, offer NRT, and request an urgent full blood count (FBC) including haematocrit. Ask the patient to withhold from gel application or injection just until the haematocrit has been established in case they require immediate venesection. If HCT > 0.6, stop treatment and contact a local haematologist urgently. If HCT < 0.6, treatment may resume with guidance from the Welsh Gender Team via the clinical e-link.
3.1 Baseline blood investigations before starting treatment
Full blood count (FBC), liver function test (LFT), HbA1c*, fasting lipids, prolactin, luteinising hormone (LH), follicle-stimulating hormone (FSH), testosterone, estradiol, sex hormone-binding globulin (SHBG), and vitamin D. Renal function if indicated.

3.2 Monitoring during titration
Blood testing schedules depend on the type of testosterone being used and are illustrated in Appendix 2. Record blood pressure, body mass index (BMI) and smoking status, ideally at each clinical review.

For all formulations of testosterone, monitoring blood is tested for FBC, LFT, fasting lipids and testosterone.

It is advisable to repeat the test if an unexpectedly high or low testosterone result is observed and check patient compliance with timing and administration before making any dose adjustments.

3.3 Testosterone gel
Examples of products currently on the market include:

- Testogel® 16.2 mg/g
- Testavan® 20mg/g
- Tostran® 2%

Tostran® is required in higher volumes and so tends only to be used in the treatment of those non-binary individuals who require a bespoke low-dose arrangement. Tostran® can also be used as a short-term measure if other options are out-of-stock.

The complete dose should be administered in one aliquot, and applied to the shoulders, arms or abdomen. Advise your patient to wash their hands with soap after each application, and to cover the area with clothing to avoid skin-to-skin transfer†.

The starting dose is usually approximately 40 mg daily.

This is equivalent to 2 pumps daily of Testogel®/Testavan® or 4 pumps daily of Tostran®.

After 10 weeks, perform blood monitoring ahead of a 12-week review. Withdraw blood 4–6 hours after gel is applied. Advise the patient not to apply the gel to the arms or shoulders on the day of the test.

Increase the dose by approximately 20 mg daily every 12 weeks until serum testosterone level in target range, to a maximum of 80 mg daily.

- Testosterone target range 15-20 nmol/L

Once in range, and if treatment is well tolerated, the patient may consider switching to the long-acting testosterone injection (Nebido®). Follow the loading schedule detailed in Section 3.5.

If gel is the patient’s preferred long-term option, once in range, upward titration can usually stop, and a check blood test performed 3 months later. If two consecutive tests are in range, the patient may move to a 6-monthly blood test. If two consecutive 6-monthly tests are in range, they can move to annual monitoring.

* Except in the case of a known haemoglobinopathy; request fasting glucose.
† Gel should be administered in accordance with the guidance provided in the manufacturer’s Summary of Product Characteristics.
3.4 Short-acting injectable testosterone

Although described in detail in this section, short-acting injectable testosterone is generally only recommended where gel therapy is not advised, e.g. in severe skin sensitivity, in circumstances where there is a significant risk of skin-to-skin transfer, etc. This is partly due to the higher rates of polycythaemia observed.

The most commonly used product on the market is Sustanon®, which also has a license for use in this context and is the preparation of choice.

The unlicensed alternative product, Delatestryl® (Testosterone enanthate), is used at an equivalent dose for patients with allergy to nut or soy.

[Note that Sustanon is advised for patients with an allergy to sesame.]

The starting dose for either product is 250 mg (1 ml) by intramuscular injection every 4 weeks.

Monitoring bloods are first performed on the day of the fourth injection and one week later to capture trough and peak testosterone readings, respectively.

- **Trough level** (for FBC, testosterone, LFT) – on the day of injection, before administration
  - **Trough testosterone target range** 8–12 nmol/L
  - Report trough level > 20 nmol/L to the Welsh Gender Team

- **Peak level** (for serum testosterone only) – one week after injection
  - **Peak testosterone target range** 25–30 nmol/L
  - Report peak level > 40 nmol/L to the Welsh Gender Team

Trough range is secured by adjusting the injection frequency by one week in either direction. Peak range is secured by adjusting the dose by 50 mg (0.2 ml) each time. If both the trough and the peak need adjustment, both the frequency and the dose may be adjusted simultaneously, and blood re-tested again around the fourth injection.

**Example 1**: if a trough reading is 6 nmol/L and peak is 26 nmol/L, the injection frequency is reduced to every 3 weeks and blood testing (trough and peak) performed again around the time of the fourth injection. The dose would remain unchanged.

**Example 2**: if a trough reading is 11 nmol/L and peak is 34 nmol/L, the injection dose is reduced by 50 mg to 200 mg (0.8 ml), but the frequency maintained at every 4 weeks and blood testing (trough and peak) performed again around the time of the fourth injection.

**Example 3**: if a trough reading is 14 nmol/L and peak is 34 nmol/L, the injection frequency is extended to every 5 weeks and the dose lowered by 50 mg to 200 mg (0.8 ml) to give a regimen of 200 mg every 5 weeks, with blood testing performed again around the time of the fourth injection.

Once in range, and if treatment is well tolerated, the patient should be encouraged to switch to the long-acting testosterone injection (Nebido®). This is started on the day their next Sustanon® injection is due, following the loading schedule in Section 3.5.

For patients who continue Sustanon® treatment, most settle at an injection interval of 2–4 weeks and a dose of 150–250 mg (0.6–1 ml). If two consecutive trough/peak blood tests are in range around the fourth injection, this can be extended to two trough/peak tests around the eighth injection, then onward to annual testing. Self-administration, if feasible, reduces the demand on primary care resources in this context.
3.5 Moving to a long-acting injectable testosterone

*Nebido*® (1000 mg/4 ml) is the most commonly used product on the market and must be administered in a healthcare setting. It is not associated with such wide variation in testosterone blood levels, it has lower rates of polycythaemia than other preparations, and it only needs to be given approximately every 3 months. This makes it the long-term treatment of choice for most patients requiring full virilisation.

For those wishing to move on to *Nebido*®, it is common practice to do so once they have spent time getting accustomed to a short-acting agent and there have been no unwanted side effects or monitoring blood abnormalities.

With this therapy, only the dosing interval is adjusted and therefore only a trough reading is required. The dose (1,000 mg/4 ml) is fixed.

- **Trough testosterone target range 15–20 nmol/L**

Blood is withdrawn on the day the injection is due, before administration. If for practical reasons this is not possible, test up to two days before.

To progress a patient from short-acting therapy onto *Nebido*®, the following loading schedule is recommended:

<table>
<thead>
<tr>
<th>Start: Nebido® 1g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 6: Nebido® 1g, + blood test for FBC</td>
</tr>
<tr>
<td>Week 18: Nebido® 1g, + blood test for FBC</td>
</tr>
<tr>
<td>Week 30: Nebido® 1g, + blood test for FBC, LFT, fasting lipids and testosterone on the day of (or up to two days before) this injection, before administration.</td>
</tr>
</tbody>
</table>

The frequency of further *Nebido*® injections is then set according to the trough testosterone reading. If it falls outside the target range, adjust the frequency by one week in either direction from the standard 12-week interval. For most patients, the dosing interval usually settles somewhere between 11–13 weeks.

If an interval adjustment is required, the trough testosterone level along with FBC and LFT are re-checked on the day of (or up to two days before) the third scheduled injection at this interval.

Once in target range, perform a confirmatory trough test with the next injection. Testing can then be extended to every other injection (approximately 6 months), and if this is stable on two occasions the patient can move to annual monitoring.

Report trough testosterone level > 25 nmol/L to the Welsh Gender Team.

*Example 1*: if a trough reading is 16 nmol/L, maintain patient at 12-weekly *Nebido*® and re-test blood on the day of (or up to two days before) the next injection, before administration to confirm.

*Example 2*: if a trough reading is 23 nmol/L, extend to 13-weekly *Nebido*® and re-test blood on the day of (or up to two days before) the third scheduled injection at this interval, before administration.

*Example 3*: if a trough reading is 11 nmol/L, reduce to 11-weekly *Nebido*® and re-test blood on the day of (or up to two days before) the third scheduled injection at this interval, before administration.

*Example 4*: if a trough reading is 27 nmol/L, report to Welsh Gender Team for further guidance.
3.6 Long-term monitoring
A patient’s testosterone therapy can be considered to be ‘optimised’ when two consecutive tests are in range approximately 3 months apart (two consecutive Nebido® injections), followed by two consecutive tests approximately 6 months apart (alternate Nebido® injections). At this stage annual blood monitoring is sufficient and the patient can be considered for discharge to their GP for ongoing maintenance prescribing under the Directed Enhanced Service.

The Directed Enhanced Service (Appendix 1) supports an annual blood test with a 30-minute clinical review. Components of the clinical review are detailed within the specification and include recording blood pressure, BMI and smoking status.

The annual blood test includes FBC, LFT, testosterone, HbA1c* and fasting lipids.

Treatment with testosterone is usually continued life-long unless medical contraindications arise; dose reduction is not justified based on age alone. The decision to discontinue therapy should be made in collaboration with the patient and the Welsh Gender Team.

Patients, and their GP, should be aware that automatic call-up to National Screening Programs will reflect the gender marker on the patient’s primary care record. Non-binary individuals assigned female at birth might also change their gender marker to one which excludes them from being invited to attend screening appropriate to their needs.

Long-term health screening should include self-examination for chest lumps (even after bilateral mastectomy and chest reconstruction surgery), breast screening if breasts are present, bowel screening, and cervical screening if the cervix is present. Trans men on long term testosterone therapy should consider attending for abdominal aortic aneurysm (AAA) when invited. Information for transgender service users can be accessed on the Public Health Wales ‘Screening for Life’ website[^10]. Any required screening tests can be arranged by either the GP or the patient.

There is a theoretical risk of endometrial hyperplasia through the action of low levels of estradiol (aromatised from testosterone) unopposed by progesterone. While the uterus is present, the current recommendation is that trans-abdominal ultrasound scanning to assess the endometrium should start after 2 years of testosterone therapy and continue on a biennial basis. To ensure continuity of care and for practical reasons this should ideally be requested by the patient’s GP, referring any suspected abnormalities to the Welsh Gender Team.

[^10]: Except in the case of a known haemoglobinopathy; request fasting glucose.
### Table 1. Testosterone therapy – summary of precautions

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>Cautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>Epilepsy</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Migraine</td>
</tr>
<tr>
<td>Breast feeding</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Primary liver tumour</td>
<td>Predisposition to oedema</td>
</tr>
<tr>
<td>Hypercalcaemia</td>
<td>Liver disease</td>
</tr>
<tr>
<td>Acute or recent arterial disease</td>
<td>Renal insufficiency</td>
</tr>
<tr>
<td></td>
<td>Obstructive sleep apnoea</td>
</tr>
<tr>
<td></td>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td>Drug interactions</td>
<td></td>
</tr>
<tr>
<td>For a comprehensive list consult the BNF or the Summary of Product Characteristics(^3,5,7,9)</td>
<td></td>
</tr>
<tr>
<td>Warfarin – testosterone may enhance anticoagulant effect.</td>
<td></td>
</tr>
<tr>
<td>Adverse drug reactions</td>
<td></td>
</tr>
<tr>
<td>For a comprehensive list (including rare and very rare adverse effects), or if significance of possible adverse event is uncertain, consult the Summary of Product Characteristics or BNF.</td>
<td></td>
</tr>
<tr>
<td>The side effect profile and safety of testosterone in trans men is identical to that seen in cisgender males undergoing testosterone replacement for hypogonadism. If you suspect an adverse reaction has occurred, report this to the specialist team. Any serious adverse reactions should also be reported to the MHRA through the &quot;Yellow Card&quot; scheme.</td>
<td></td>
</tr>
<tr>
<td>Clinical condition</td>
<td>Management</td>
</tr>
<tr>
<td>Local irritation</td>
<td>Rotate application/injection sites.</td>
</tr>
<tr>
<td>Mood fluctuations</td>
<td>Particularly with the short-acting injectable formulation given the more pronounced peaks and troughs.</td>
</tr>
<tr>
<td>Polycythaemia</td>
<td>Testosterone therapy stimulates erythropoietin production(^11). Seek advice from Welsh Gender Team if haematocrit &gt;0.52. Stop and seek urgent advice from a haematologist if haematocrit &gt;0.60</td>
</tr>
<tr>
<td>Obstructive sleep apnoea</td>
<td>Testosterone therapy may exacerbate the symptoms of obstructive sleep apnoea. Refer to a specialist in sleep disorders if the patient's condition deteriorates.</td>
</tr>
<tr>
<td>Abnormal lipid profile</td>
<td>Testosterone replacement in trans-men is associated with an increase in triglycerides and a decrease in plasma HDL levels. However, these changes do not appear to alter cardiovascular mortality(^12). Normal cardiovascular risk assessment applies.</td>
</tr>
<tr>
<td>Future fertility</td>
<td>Patients are counselled that treatment with testosterone may temporarily or permanently impair fertility and counselled about their future reproductive options.</td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td>LFT abnormalities are usually minor and do not require treatment to be stopped. An increase in liver enzymes to more than three times the upper limit of normal requires suspension of treatment; contact the Welsh Gender Team.</td>
</tr>
</tbody>
</table>
4.0 ESTROGEN THERAPY – PRESCRIBING NOTES

Estrogen-only hormone replacement therapy (HRT) is the mainstay of medical treatment in trans women. This is introduced gradually and titrated to achieve a serum estradiol level of 350–750 pmol/L.

Although endogenous testosterone release is suppressed, estrogen therapy alone is not usually sufficient to lower it into the female range of serum testosterone 0-3 nmol/L. The use of GnRH agonists and other anti-androgen treatment are covered in Section 5.0.

Some (but not all) non-binary individuals who were assigned male at birth opt for low dose estrogen (estradiol) therapy under specialist guidance.

Estradiol is neither a contraceptive nor does it prevent sexually transmitted infections.

Smoking increases the risk of thrombosis, so cessation should be strongly encouraged. The decision to commence treatment in a patient who smokes should be made by the Welsh Gender Team.

Before starting estradiol therapy, a patient should ideally have stopped smoking for a minimum of 3 months. Nicotine replacement therapy (NRT) is considered a safe alternative in this scenario. It is good practice to document smoking status at each clinical review*.

Estradiol is usually suspended 6 weeks before any surgery that may result in immobility and resumed at their pre-operative dose in accordance with advice from the surgical team (usually 4–6 weeks post-operatively).

Inform the Welsh Gender Team if a patient has had a break from estradiol treatment of longer than 6 months.

4.1 Baseline blood investigations before starting treatment
FBC, LFT, HbA1c†, fasting lipids, prolactin, LH, FSH, testosterone, estradiol, SHBG, and vitamin D. Prostate-specific antigen (PSA) in patients aged 40 years and older. Renal function if indicated.

4.2 Monitoring during titration
Blood testing schedules are illustrated in Appendix 2.

For all types of estradiol, monitoring blood tests are performed every 10 weeks ahead of a 12-week review during the initiation phase. Once serum estradiol is in the desired range, upward titration can stop, and a check blood test performed 3 months later. If two consecutive tests are in range, the patient may move to a 6-monthly blood test. If two consecutive 6-monthly tests are in range, they can move to annual monitoring. Record blood pressure, BMI and smoking status at each clinical review.

For all forms of estradiol, monitoring blood is tested for LFT, prolactin, estradiol, and testosterone.

It is advisable to repeat the test if an unexpectedly high or low estradiol result is observed and check patient compliance with timing and administration before making any dose adjustments.

* If a patient reports that they have resumed smoking, encourage cessation, offer NRT and contact the Welsh Gender Team for further guidance.
† Except in the case of a known haemoglobinopathy; request fasting glucose.
4.3 Oral estradiol therapy
Oral therapy is usually first line unless it is medically contraindicated, or the patient is obese, a smoker, or would prefer a topical agent. Oral options include:

- Estradiol valerate (Progynova®)
- Estradiol hemihydrate (Elleste Solo®, Zumenon®)

Ethinylenestradiol has been demonstrated to alter the levels of plasma protein S, C and prothrombin and should not be used. Most patients start at 2 mg daily; full dose to be taken at once, in the morning, swallowed whole.

After 10 weeks perform monitoring bloods ahead of a 12-week review. Withdraw blood 4–6 hours after tablet(s) taken.

- Serum estradiol target range 350–750 pmol/L

Increase the dose by 2 mg every 12 weeks according to response, up to a maximum of 8 mg daily. If the target range is not reached after 3 months of oral treatment at a dose of 6 mg daily, the patient may wish to consider switching to topical therapy as described in Section 4.4. This bypasses liver metabolism and usually achieves higher blood levels.

If the patient prefers to stay on tablets but fails to reach target range after 3 months of oral treatment at 8 mg daily, contact the Welsh Gender Team for guidance.

4.4 Topical estradiol therapy
Topical estradiol is used when oral therapy is not tolerated, is medically contraindicated, or it fails at higher doses to achieve the desired target range. It is considered first-line for patients with obesity and in those who continue to smoke, and it can be recommended for the older patient.

Topical therapy options include transdermal gel (e.g.: Sandrena®), and patches (e.g.: Evorel®, Estradot®), and should be guided by patient preference.

4.4.1 Estradiol gel
The complete dose should be administered in one aliquot, applied anywhere on the body except for the breasts. Patients are advised to wash their hands with soap after each application, and to cover the area with clothing to avoid skin-to-skin transfer*. Most patients start at 1 mg daily. This is equivalent to 2 mg of the oral dose.

After 10 weeks, perform monitoring bloods ahead of a 12-week review. Withdraw blood 4–6 hours after the gel is applied. Advise the patient not to apply gel to the arms or shoulders on the day of the test.

- Serum estradiol target range 350–750 pmol/L

Increase the dose by 1 mg every 12 weeks according to response, to a maximum of 4 mg daily. If the target range for estradiol is not achieved after 3 months of gel treatment at 4 mg daily, contact the Welsh Gender Team for guidance.

4.4.2 Estradiol patches
Patches can be applied anywhere on the body except for the breasts. It is worth noting that some brands are affected by exposure to sunlight, and application to the waistline may also risk patches being rubbed off by clothing.

* Gel should be administered in accordance with the guidance provided in the manufacturer’s Summary of Product Characteristics.
Endocrine Management of Gender Dysphoria in Adults

Start at 50 micrograms/24 h twice-weekly. This is equivalent to 2 mg daily of the oral dose.

After 10 weeks, perform monitoring bloods. Withdraw blood **48 hours** after a new patch is applied and advise the patient not to apply it to the arms or shoulders on this occasion.

- **Serum estradiol target range 350–750 pmol/L**

Increase the dose by 50 micrograms/24 h twice weekly every 12 weeks according to response, up to a maximum of 200 micrograms/24 h twice-weekly. If target range is not achieved after 3 months of patch treatment at 200 micrograms/24 h twice-weekly, contact the Welsh Gender Team for guidance.

4.5 Switching from oral estradiol to topical therapy

With topical agents, higher estradiol levels are expected to be achieved with lower doses. When switching from oral to topical treatment, it is not uncommon to start the patient on the topical dose equivalent to 2 mg less than their current oral dose.

For example, if the patient is taking 6 mg oral estradiol, start with a topical dose equivalent to 4 mg oral estradiol. This would be a 2 mg daily sachet of Sandrena® gel, or a 100 microgram twice-weekly patch (Evorel®, Estradot®).

Perform a monitoring blood test at 10 weeks, reviewing at 12 weeks to see if further titration is needed.

4.6 Long-term monitoring

A patient’s estrogen therapy can be considered to be ‘optimised’ when two consecutive tests are in range 3 months apart, followed by two consecutive tests 6 months apart. At this stage, annual blood monitoring is sufficient and the patient can be considered for discharge to their GP for ongoing maintenance prescribing under the Directed Enhanced Service.

The Directed Enhanced Service (Appendix 1) supports an annual blood test with a 30-minute clinical review. Components of the clinical review are detailed in the specification and include recording blood pressure, BMI and smoking status.

The annual blood test includes **LFT, prolactin, estradiol, testosterone**, **HbA1c†**, and **fasting lipids**.

Estradiol use in trans women over 55 years of age appears safe from the point of view of breast health, and most continue HRT lifelong unless medical complications arise.

Older patients who wish to reduce their estradiol dose may do so. A dose that reflects a serum estradiol level of 200-300 pmol/L should be adequate to maintain feminisation and bone density.

The decision to discontinue therapy should be made in collaboration with the patient and the Welsh Gender Team.

Patients, and their GPs, should be aware that automatic call-up to National Screening Programs will reflect the gender marker on the patient’s primary care record. Non-binary individuals assigned male at birth might also change their gender marker to one which excludes them from being invited to attend screening appropriate to their needs.

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* If your patient is using a GnRH agonist or has undergone genital surgery involving orchidectomy, repeated testing of serum testosterone is not usually required.
† Except in the case of a known haemoglobinopathy; request fasting glucose.
Encourage all women to be breast aware. Long-term health screening should include breast, bowel, and AAA screening. Information for transgender service users can be accessed on the Public Health Wales ‘Screening for Life’ website. Any required screening tests can be arranged by either the GP or the patient.

### Table 2. Estradiol therapy – summary of precautions

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>Cautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>Obesity</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>Hypertension</td>
</tr>
<tr>
<td>• active</td>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td>• recurrent</td>
<td>Single DVT</td>
</tr>
<tr>
<td>Thrombophilic disorders</td>
<td>Family history of thromboembolism and breast cancer</td>
</tr>
<tr>
<td>Dubin-Johnston and Rotor syndromes</td>
<td>Migraine with focal neurology</td>
</tr>
<tr>
<td>Acute liver disease</td>
<td>SLE</td>
</tr>
<tr>
<td>Acute or recent arterial disease</td>
<td>Sickle cell disease</td>
</tr>
<tr>
<td>Acute porphyria</td>
<td>Gallstones and liver disorders</td>
</tr>
</tbody>
</table>

#### Drug interactions

For a comprehensive list consult the BNF or Summary of Product Characteristics.

There are no drug interactions with topical estradiol. The metabolism of oral estradiol can be affected by drugs which act on liver enzymes, such as cytochrome P450. Both enzyme inducers and inhibitors have been shown to have enzyme-inducing properties when used concomitantly with steroid hormones.

#### Adverse drug reactions

For a comprehensive list (including rare and very rare adverse effects), or if the significance of a possible adverse event is uncertain, consult the Summary of Product Characteristics or BNF.

Although higher doses are used, estrogen is usually very well tolerated. If you suspect an adverse reaction has occurred this should be reported to the specialist team. Any serious reaction should also be reported to the MHRA through the "Yellow Card" scheme.

<table>
<thead>
<tr>
<th>Clinical condition</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolic disease</td>
<td>DVT risk is dramatically reduced with newer estrogen formulations. Advise patients to report symptoms urgently.</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Risk of breast cancer secondary to estrogen therapy is thought to be lower than for cisgender women. However, uptake of the National Breast Screening program is strongly advised.</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Incidence is reduced secondary to estrogen therapy, but symptoms should be investigated.</td>
</tr>
<tr>
<td>Fertility impairment</td>
<td>Estrogen therapy can lead to a reduction in spermatogenesis. Patients are counselled that treatment might affect their fertility and are offered sperm storage before starting treatment.</td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td>LFT abnormalities are usually minor and do not require stopping treatment. An increase in liver enzymes to more than three times the upper limit of normal requires suspension of treatment; seek advice from the Welsh Gender Team.</td>
</tr>
<tr>
<td>Hyperprolactinaemia</td>
<td>Serum prolactin may rise with the introduction of estradiol therapy. If there is a new rise of &gt; 750 mIU/L, repeat the test. If there is a new rise of &gt; 1,000 mIU/L, repeat the test and inform the Welsh Gender Team.</td>
</tr>
</tbody>
</table>
5.0 GONADOTROPHIN-RELEASING HORMONE AGONIST AND ANTI-ANDROGEN TREATMENTS – PRESCRIBING NOTES

These treatments are sometimes an important component of the medical transition process, particularly for trans women requiring further androgen suppression. Some (but not all) non-binary individuals assigned male at birth use anti-androgen monotherapy under specialist guidance.

5.1 Gonadotrophin-releasing hormone agonists

GnRH agonist medications bind to the GnRH receptor on the pituitary gland, initially stimulating, then downregulating the release of gonadotrophins (luteinizing hormone, follicle-stimulating hormone). With the hypothalamic-pituitary-gonadal (HPG) axis switched off, sex hormone production from the gonads falls significantly.

GnRH agonists are used by trans women who require a low testosterone, as estrogen treatment alone is often not sufficient to suppress testosterone into the female range 0–3 nmol/L.

Patients intending to undergo genital surgery involving orchidectomy require full suppression of testosterone (< 3 nmol/L) for at least 9 months as a pre-requisite and this can only usually be achieved with the administration of a GnRH agonist injection. The treatment provides an opportunity for a patient to experience the castrate hormone milieu in a reversible way. Post-operatively, a GnRH agonist is no longer required.

To avoid triggering menopausal symptoms, GnRH agonist treatment is introduced once the patient’s endogenous sex steroid levels are approaching target range. In the case of trans women, serum estradiol is usually sufficient after 3 months of treatment at an oral dose of 4 mg estradiol daily (or equivalent topical dose).

For trans women, the first GnRH agonist injection is thought to cause a brief, one-off testosterone flare as GnRH receptors (and production of LH and FSH) are stimulated. Symptoms of this flare are counteracted by the co-administration of Cyproterone acetate 100 mg once daily for 14 days with the first GnRH agonist injection only. After this, gonadal testosterone production is switched off and remains so for the duration of treatment.

Recommended GnRH agonists:

- **Triptorelin (Decapeptyl®)** 11.25 mg intramuscularly every 12 weeks\(^{22}\).
- **Leuprorelin (Prostap®)** 11.25 mg intramuscularly every 12 weeks\(^{23}\).

Alternative GnRH agonist:

- **Goserelin (Zoladex®)** 10.8 mg subcutaneously every 12 weeks\(^{24}\).

All are available as monthly preparations if indicated or preferred.

Once testosterone suppression has been confirmed, or after genital surgery involving orchidectomy, routine monitoring of serum testosterone is no longer necessary.

In the context of prescribing a GnRH agonist for trans men, if the use of a progestin fails to abolish menstruation or the discomfort of anovulatory cycling, this treatment is very effective. Seek advice from the Welsh Gender Team.
Table 3. GnRHa therapy – summary of precautions

<table>
<thead>
<tr>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity to GnRH, its analogues or any other component of the medicinal product</td>
</tr>
</tbody>
</table>

**Drug interactions**
For a comprehensive list consult the BNF or the Summary of Product Characteristics

Androgen suppression can prolong QT interval therefore concomitant use of medication known to prolong the QT interval should be used with care. An ECG should be done to assess baseline QT interval.

**Adverse drug reactions**
For a comprehensive list (including rare and very rare adverse effects), or if significance of possible adverse event uncertain, consult the Summary of Product Characteristics or BNF.

This treatment is well tolerated and generally not associated with significant side effects. The use of GnRH agonists in conjunction with cross-sex hormone therapy mitigates menopausal symptoms, cardiovascular risk and bone demineralisation. Some patients report short-lived musculoskeletal aching immediately after each injection which resolves after one or two days. Low energy, drive, or sexual desire should be reported to the Welsh Gender Team. If you suspect an adverse reaction has occurred this should be reported to the Welsh Gender Team. Any serious reaction should also be reported to the MHRA through the “Yellow Card” scheme.

5.2 Finasteride

Finasteride\(^{25}\) is a less potent oral alternative to a GnRH agonist for use in patients assigned male at birth.

Finasteride inhibits 5-alpha reductase, preventing conversion of testosterone into the more potent dihydrotestosterone (DHT). In this setting it is used at a dose of 5 mg daily.

It can be considered as an alternative to a GnRH agonist for patients who do not require their testosterone to be fully suppressed into the female range, for example, those wishing to retain some libido and erectile function.

Finasteride also helps to minimise scalp hair loss, offering long-term protection for those at risk. It can be continued after genital surgery involving orchidectomy as a small amount of testosterone is secreted by the adrenal glands.

Table 4. Finasteride – summary of precautions

<table>
<thead>
<tr>
<th>Drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>For a comprehensive list consult the BNF or the Summary of Product Characteristics</td>
</tr>
</tbody>
</table>

No relevant drug interactions.

**Adverse drug reactions**
For a comprehensive list (including rare and very rare adverse effects), or if significance of possible adverse event uncertain, consult the Summary of Product Characteristics or BNF.

<table>
<thead>
<tr>
<th>System</th>
<th>Frequency</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Not known</td>
<td>Hypersensitivity reactions, including pruritus, rash, urticaria, and swelling of the lips and face</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Not known</td>
<td>Palpitations</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Uncommon (≥1/1,000 to &lt;1/100)</td>
<td>Decreased libido</td>
</tr>
<tr>
<td></td>
<td>Uncommon (≥1/1,000 to &lt;1/100)</td>
<td>Depressed mood</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Not known</td>
<td>Increased hepatic enzymes</td>
</tr>
</tbody>
</table>

If you suspect an adverse reaction has occurred this should be reported to the Welsh Gender Team. Any serious reaction should also be reported to the MHRA through the “Yellow Card” scheme.
### 6.0 WELSH GENDER SERVICE CONTACT INFORMATION

| Mobile number for endocrine advice (11.30–14.30): | 07971529080 |
| Phone number for general enquiries: | 02921 836612 |
| Phone number for appointment enquiries: | 02921 847548 |
| Email for endocrine enquiries: | cav.wgs@wales.nhs.uk |
| Email for all other enquiries: | cav.wgs_enquiries@wales.nhs.uk |

**Address:** Welsh Gender Service  
St David’s Hospital  
Cowbridge Road East  
Cardiff  
CF11 9XB
REFERENCES


APPENDIX 1 DETAILS OF THE DIRECTED ENHANCED SERVICE

The document detailing the Directed Enhanced Service for the Hormone Treatment Scheme for Adult Transgender Patients in NHS Wales (published 20 August 2019) is included on pages 21–27.

The Directed Enhanced Service document refers to Appendices A, B, C and D, which can be accessed here.
THE NATIONAL HEALTH SERVICE (WALES) ACT 2006

The Primary Medical Services (Hormone Treatment Scheme for Adult Transgender Patients) (Directed Enhanced Service) (Wales) Directions 2019

Made 20 August 2019

Coming into force 01 September 2019

The Welsh Ministers, in exercise of the powers conferred by sections 12(3), 45, 203(9) and (10) of the National Health Service (Wales) Act 2006,(1) and after consulting in accordance with section 45(4) of that Act with the bodies appearing to them to be representative of persons to whose remuneration these Directions relate, give the following Directions.

Title, commencement and application

1.—(1) The title of these Directions is the Primary Medical Services (Hormone Treatment Scheme for Adult Transgender Patients) (Directed Enhanced Service) (Wales) Directions 2019.

(2) These Directions come into force on 01 September 2019.

(3) These Directions are given to Local Health Boards.

Interpretation

2. In these Directions—

“the Act” (“y Ddeddf”) means the National Health Service (Wales) Act 2006;

(1) 2006 c. 42.
“cluster” (“clwstwr”) has the same meaning as paragraph 3.4 of the Hormone Treatment Scheme for Adult Transgender Patients Specification(1); “cluster lead practice” (“practis arweiniol y clwstwr”) means a GMS contractor that has agreed to provide this Directed Enhanced Service to its registered patients, and to the registered patients of a GMS contractor in its cluster that is not an engaged GMS contractor, and which the Local Health Board agrees will be a cluster lead practice; “engaged GMS contractor” (“contractiwr GMS â chytundeb”) means a GMS contractor that agrees with a Local Health Board to provide this Directed Enhanced Service pursuant to an agreement made in accordance with paragraph 4(1); “financial year” (“blwyddyn ariannol”) means the period from 1 April to 31 March in any year; “general medical services contract” (“contractau gwasanaethau meddygol cyffredinol”) means a contract for general medical services between a GMS contractor and a Local Health Board made pursuant to section 42 of the Act; “GMS contractor” (“contractwr GMS”) means a person with whom a Local Health Board is entering or has entered into a general medical services contract; “health care professional” (“gweithiwr gofal iechyd proffesiynol”) means a person who is a member of a profession regulated by a body mentioned in section 25(3) of the National Health Service Reform and Health Care Professions Act 2002(2); “Hormone Treatment for Adult Patients Specification” (“Manyleb Triniaethau Hormonau i Oedolion o Gleifion”) means the Specification for Hormone Treatment for Adult Patients with Gender Dysphoria/Incongruence after Assessment and Optimisation of Treatment by the Welsh Gender Clinic and Local Intermediate Gender Team [http://www.wales.nhs.uk/sites3/page.cfm?orgid=480&pid=82636]; “registered patient” (“cleifion cofrestredig”) has the meaning given to it in regulation 2(1) of the National Health Service (General Medical Services Contracts) (Wales) Regulations 2004(3); “Statement of Financial Entitlements” (“Datganiad ar Hawlogaeth Ariannol”) means any

(1) The Hormone Treatment for Adult Transgender Patients Specification is available here [http://www.wales.nhs.uk/sites3/page.cfm?orgid=480&pid=82636];
(2) 2002 c. 17.
(3) S.I. 2004/478 (W. 48).
directions given by the Welsh Ministers pursuant to section 45 of the Act in relation to payments to be made by a Local Health Board to a GMS contractor.

Establishment of a Hormone Treatment Scheme for Adult Transgender Patients

3.—(1) Each Local Health Board is required under section 41 of the Act (primary medical services) to exercise its functions so as to provide, or secure the provision of, primary medical services within its area.

(2) As part of its discharge of its functions under section 41 of the Act each Local Health Board must establish (if it has not already done so), operate and, as appropriate, revise a Hormone Treatment Scheme for Adult Transgender Patients.

(3) The underlying purpose of the Hormone Treatment Scheme for Adult Transgender Patients is to ensure appropriate support for adult patients (aged 18 and over) who require ongoing hormonal therapy after the local gender care team have—

(a) initiated and optimised a patient’s hormone treatment, and

(b) completed the transfer of care document at Appendix D to the Hormone Treatment for Adult Patients Specification.

Hormone Treatment Scheme for Adult Transgender Patients

4.—(1) As part of its Hormone Treatment Scheme for Adult Transgender Patients, each Local Health Board must offer to enter into arrangements for the provision of services in accordance with the Hormone Treatment for Adult Patients Specification with—

(a) each GMS contractor, in relation to the registered patients of that GMS contractor; and then

(b) one or more cluster lead practices, in relation to the registered patients of the cluster lead practice and the patients of those GMS contractors, if any, in its cluster that have not agreed, within such time period as the Local Health Board requires, to deliver this Directed Enhanced Service to their registered patients pursuant to paragraph 4(1)(a) above.

(2) Where the patients of a GMS contractor will not receive the services outlined in this Directed Enhanced Service, either from the GMS contractor in relation to whom they are registered patients, or from a cluster lead practice, the Local Health Board must make arrangements to ensure the provision of treatment to the registered patients of that GMS contractor as close to the practice premises of that GMS contractor as is
reasonably practicable and the Local Health Board may deliver the services under this Directed Enhanced Service to those patients in any way it believes is appropriate (including, but not limited to, by providing the services itself or arranging for the delivery of those services by any engaged GMS contractor).

(3) Where arrangements are made between a cluster lead practice and a Local Health Board in accordance with paragraph (1)(b), each engaged GMS contractor must co-operate(1) with the other engaged GMS contractors and the cluster lead practice in its cluster in order for the cluster lead practice to complete, by such date as the Local Health Board requires, a plan setting out the arrangement for the delivery of this Directed Enhanced Service to patients of the engaged GMS contractors across the cluster. Where there is only one engaged GMS contractor, and it is the cluster lead practice, it shall be responsible for completing that plan. Where there is no cluster lead practice, and all of the GMS contractors in the cluster are engaged GMS contractors, they shall all be responsible for completing that plan.

(4) Where arrangements are made between the Local Health Board and a GMS contractor pursuant to paragraph (1), those arrangements must, in respect of each financial year (or part of a year) to which they relate, include—

(a) a requirement that the GMS contractor—

(i) reads and takes account of these Directions alongside complying with the Hormone Treatment for Adult Patients Specification and its appendices which together provide the detailed requirements for this Directed Enhanced Service;

(ii) maintains and keeps up to date a register of all patients receiving treatment under this Directed Enhanced Service;

(iii) provides the services outlined in the Hormone Treatment for Adult Patients Specification and in line with the plan specified in paragraph (3) above;

(iv) provides data, subject to paragraph (v) below, to the cluster lead practice of a cluster (where applicable), Local Health Boards and Welsh Government when required to inform the design and development of services for adult patients with Gender Dysphoria / Incongruence;

(1) See paragraph 12 of Part 1 of Schedule 6 to the National Health Service (General Medical Services Contracts) (Wales) Regulations 2004 (S.I. 2004/478 (W.48)).
(v) ensures consistent coding for capture of data and compliance with relevant information governance legislation;

(vi) ensures that each healthcare professional undertaking this Directed Enhanced Service has the necessary skills, training, competence and experience in order to provide the services;

(vii) ensures each healthcare professional undertaking this Directed Enhanced Service completes relevant CPD activity through, for example, regular educational updates, attendance at relevant courses provided by the Local Health Boards, as well as self-directed learning, to be able to demonstrate they have adequate knowledge and skills through their annual appraisal and revalidation;

(viii) ensures that each healthcare professional undertaking this Directed Enhanced Service considers any offer of educational update courses provided by the Local Health Board;

(ix) ensures that each healthcare professional undertaking this Directed Enhanced Service is adequately indemnified / insured for any liability arising from the work performed;

(x) gives three months’ notice in writing prior to terminating their provision of this Directed Enhanced Service;

(xi) supplies its Local Health Board with such information as the Local Health Board may reasonably request for the purposes of monitoring the engaged GMS contractor’s performance of its obligations under this Directed Enhanced Service, and the cluster’s performance in relation to the plan specified in paragraph (3) above;

(xii) completes an annual report of outcomes by 31 March each year in line with the proforma at Appendix B of the Hormone Treatment Specification for Adult Patients

(b) payment arrangements for an engaged GMS contractor, which must provide for it to be able to claim (whether acting just for itself or as a cluster lead practice)—

(i) a one-off practice preparatory payment of £250 (where a practice acts as a cluster lead practice, they will only be entitled to receive £250, this sum will not be multiplied by the number of practices on
behalf of which the cluster lead practice will deliver the DES);

(ii) a payment of £100 per annum for each patient for whom the GMS contractor undertakes an annual review required by paragraph 12.1 of the Hormone Treatment for Adult Patients Specification (paid as a single payment after the review has taken place);

(iii) a payment of £110 per annum for the administration, once every three months, of gonadorelins (to be paid in four instalments, quarterly in arrears);

(iv) a payment of £110 per annum for the administration, once every 3 months, of testosterone injections (to be paid in four instalments, quarterly in arrears)

and after the payments are due, as above, and authorised by the Local Health Board, such payments will then be paid on the date the GMS contractor’s Global Sum monthly payment next falls due in accordance with the Statement of Financial Entitlements.

(5) The Local Health Board must, where necessary, vary the GMS contractor’s general medical services contract so that the arrangements made pursuant to paragraph (1) comprise part of the GMS contractor’s contract and the requirements of the arrangements are conditions of the contract.

(6) Any disputes arising as a result of provision of this Directed Enhanced Service will be dealt with in accordance with part 7 of Schedule 6 to the National Health Service (General Medical Services Contracts) (Wales) Regulations 2004(1).

(7) Where the Local Health Board delivers this Directed Enhanced Service pursuant to an arrangement in accordance with paragraph 4(2), the Local Health Board shall ensure that paragraphs 4(4) and 4(5) apply to such arrangements as they would to an engaged GMS contractor.

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(1) S.I. 2004/478 (W. 48).
Signed by Alex Slade, Acting Deputy Director, Primary Care Division under the authority of the Minister for Health and Social Services, one of the Welsh Ministers

Date: 20 August 2019
Initiation of transdermal testosterone

**Testosterone gel: approximately 40 mg daily**

If serum testosterone < 15 nmol/L

**Testosterone gel: approximately 60 mg daily**

If serum testosterone < 15 nmol/L

Consider switch to Nebido® or a further increase to max gel dose 80 mg daily

**Monitoring**
- 10 weeks
  - FBC
  - LFT
  - Fasting lipids
  - Testosterone

**Monitoring**
- 10 weeks
  - FBC
  - LFT
  - Fasting lipids
  - Testosterone

Record blood pressure, BMI, smoking status at each visit.

Gel can be applied to the upper arms, shoulders or abdomen. Wash hands with soap and cover with clothing. Avoid skin to skin contact for 6 h. Withdraw blood 4–6 h after gel applied. Do not apply to the arms/shoulders on the day of the test.

**Titrate to achieve serum testosterone 15–20 nmol/L.**

Repeat blood monitoring every 3 months until the desired range is reached, then consider Nebido® loading at the next visit if desired and provided HCl and other monitoring bloods are normal. Optimised = two consecutive readings in ideal range. Further two tests at 6 months, then annually.
Initiation of short-acting intramuscular testosterone
(Sustanon® or Delatestryl®)

- **Sustanon® 250 mg IM**
  - 4 weeks
  - **Sustanon® 250 mg IM**
  - 4 weeks
  - **Sustanon® 250 mg IM**
  - 4 weeks

**Monitoring**
- Morning of the fourth injection
  - FBC
  - LFT
  - Fasting lipids
  - Testosterone (T)

**Monitoring**
- One week after injection
  - Testosterone (P)

- **Aim for:**
  - Trough testosterone 8–12 nmol/L
  - Peak testosterone 25–30 nmol/L

If trough level > 20 nmol/L or peak level > 40 nmol/L contact Welsh Gender Team.

Record blood pressure, BMI, smoking status at each visit. Trough (T) is captured by adjusting frequency usually by one week in either direction. Peak (P) is captured by adjusting dose by 50 mg (0.2 ml) each time. Repeat blood monitoring (of trough and peak) every 4th injection until in desired range, then aim to commence Nebido® loading.

*For nut/soy allergy use Delatestryl® (testosterone enanthate). For sesame allergy use Sustanon®.
Initiation/loading of long-acting intramuscular testosterone (Nebido®)

Nebido® 1 g IM

6 weeks

Nebido® 1 g IM

12 weeks

Nebido® 1 g IM

12 weeks

Nebido® 1 g IM

? weeks
Set interval according to trough testosterone result

Nebido® reset (T > 25 nmol/L)
STOP. Measure testosterone every 2/52 until T<15 nmol/L then resume at previous interval + 1 week. Re-test trough on morning of (or up to 2 days before) third injection

Aim for trough testosterone 15–20 nmol/L

Monitoring
FBC

Monitoring
FBC

Morning of injection or up to 2 days before
FBC
LFT
Fasting lipids
Testosterone (T)

Record blood pressure, BMI, smoking status at each visit. Nebido® cannot be self-administered. If trough testosterone is outside target range, adjust dosing interval by 1 week in the appropriate direction and re-test around the time of the third injection at this interval. Once target range achieved, confirm at next Nebido® injection, then with alternate injections on two occasions, moving to annually.
Initiation of estrogen

1. Estradiol 2 mg OD (or equiv. topical) + finasteride 5 mg OD

2. If serum estradiol < 350 pmol/L
   - Estradiol 4 mg OD (or equiv. topical)

3. If serum estradiol < 350 pmol/L
   - Estradiol 6 mg OD (or equiv. topical)
     - If serum testosterone > 3 nmol/L and clinically indicated:
       - GnRHa + cyproterone acetate 100 mg OD for 14 days (with first injection only)

4. Estradiol < 350 pmol/L
   - Contact Welsh Gender Team

Monitoring
- 10 weeks
- LFT
- Prolactin
- Testosterone
- Estradiol

Record blood pressure, BMI, smoking status at each visit. Withdraw blood 4–6 h after tablet/gel, or 48 h after patch applied. **Titrate every 12 weeks to achieve serum estradiol 350–750 pmol/L.** Estradiol patch starts at 50 micrograms/24 h twice weekly and is adjusted by 50 micrograms/24 h twice weekly every 12 weeks. Estradiol gel starts at 1 mg/day and is adjusted by 1 mg/day every 12 weeks. GnRHa (usually Decapeptyl® or Prostap®) is given as a 12-week preparation but is available as a monthly preparation if requested/appropriate.